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Dr. Joshua Lederberg, President
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Dear Josh:

I just got back from a month in Japan and Australia, so am just tuning in on your essay for "Perspectives". It produced an overwhelming, but pleasurable, bout of nostalgia.

There is little to add to Bill's comments, but here are a couple of elaborations.

As for a reference to the Cairns item, your suggestion to mention it and the December 8 discussion only briefly is fine. You could point out how tricky selection can be. We both recall that the Delbruck-Luria treatment was not acceptable to all (e.g. Hinshelwood), so neither is the far less convincing Cairns paper. Something with the rigor of your methods -- particularly the one with Lucca showing that (within the precision and conditions of the experiments) spontaneous mutations were quantitatively sufficient to explain the observed results -- is needed; or a similarly inventive new approach demonstrating positively the phenomenon proposed. The problem, I think, is how to be skeptical of existing claims of adaptively directed mutation and to ask for much better evidence, while retaining an open mind as to the possibility of novel findings. I remember how popular it was in my graduate school days to invent subtle ways in which selection could account for transformation in Pneumococcus. If such a phenomenon exists, an organism that has been exposed for a very long time to environments with and without lactose would be a natural place to

look.

Regarding your comment on page 5, Bill thinks some elaboration is needed. In particular the allusion to selection based on the phenotypes of close relatives (especially for traits expressed in only one sex) may be missed. I don't recall making any jokes (although I may have), but I do recall being pleased that indirect selection, a commonplace to breeders, was being applied to the then-novel field of microbial genetics -- and moreover, being used to answer a fundamental question then being actively debated. I also remember suggesting Lush's book as a reference. I was greatly impressed with the cleverness of the whole thing; the idea might have been commonplace, but the technique and the use in this context weren't.

I want to raise a couple of other questions.

First, on April 4, 1958, I wrote Motoo a letter, which included the following paragraph:

> Have you ever considered this problem? Suppose every mutant is to an entirely different allele (or at least counted this way, so that the only homozygosity is homozygosity by descent). Under such a system with a finite population of size n what is the proportion of homozygous loci at equilibrium? Perhaps you have already solved this, but I am not sure. Some of Josh's work suggests that every mutant is distinguishable from every other one if a careful enough test is made; at least this is true for a large number.

Do you know what work of yours I might have had in mind? The reason for asking is that I am planning a "Perspectives" for April on the "infinite allele model", which had its origin in a Genetics paper 25 years ago. [This reminds me of something else, a discussion that you and I had with Muller around 1949. You were suggesting that the wild type allele might in fact be a population of indistinguishable isoalleles. After you left and as he was rushing to leave town he said he would have to leave it to me to persuade you of the error of your view! I vividly remember his saying: "You convince him".]

Second, we are planning a symposium celebrating the centennial of Sewall Wright's birth. The symposium will consist of talks on the current status of

Bill:

I am chairing an NIH sponsored conference in mid February about ways to co-ordinate and speed the human linkage map. It occurred to me that one point to raise is the use of mouse information.

Who would be a good person to invite for this purpose? Roderick? Ruddle? yourself? ? ? ?

Jim